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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/816,785	03/22/2001	Ira J. Fox	UNMC -0032	5547

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 08/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/816,785	FOX ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *1-7,9-13,15,23,24 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8, 14, 16-22, 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment and response filed June 7, 2005 have been entered. Claims 8, 14, and 25 have been amended. Claims 8, 14, 16-22, 25 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 6/7/05 response would be addressed to the extent that they apply to current rejection.

Upon further consideration, new grounds of rejection are necessitated and appear below.

Claim Objections

Claims 8, 16-22 are objected to because of the following informalities: the word "isolated" should be inserted before "population" or "immortalized" since the immortalized cells are not intended for *in vivo* use. Appropriate correction is required.

Claim 16 is objected to, it is suggested to replace "that flank" with "flanking" in order to make clear the presence of both the recombinase target sites and the oncogene.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 recites the limitation "the method of claim 16". There is insufficient antecedent basis for this limitation in the claim.

Claims 14 recites the limitation "the method of claim 25". There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 22 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

Claim 22 is drawn to a specific cell line NKNT-3 made by transfecting human primary hepatocyte with an immortalizing DNA construct. Although transfecting cells with a gene expressing vector construct is routine in the art at the time of instant effective filing date, the particular cell line bearing the customer name NKNT-3 may possess specific characteristics distinct from other transfected human primary hepatocytes. Since the recited customer name does not describe any specific characteristics of the cell line, and the specification fails to teach a reproducible method to consistently obtain a cell line bearing the same characteristics of the NKNT-3 cell line, the claimed invention is not considered as fully enabled.

Applicant is reminded an enabling deposit of the recited cell line may satisfy the requirements of 35 U.S.C. 112, first paragraph.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants, or a statement by an attorney of record over his or her signature and registration number, stating the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If a deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809 and MPEP 2402-2411.05, Applicant may provide assurance of compliance by affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number showing that:

(a) during the pendency of the application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years, or 5 years after the last request or for the enforceable life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

Claims 8, 14, 16-21, 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making an immortalized hepatocyte comprising transforming a primary hepatocyte with a retroviral vector comprising two recombinase target sites flanking an oncogene, does not reasonably provide enablement for making an immortalized hepatocyte comprising transforming a primary hepatocyte with *any* DNA construct comprising two recombinase target sites flanking an oncogene, which confers immortalization to the hepatocyte. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

This is because the immortalization process requires the DNA construct being integrated into the genome of the cell, whereas DNA constructs that remain epi-genomic would be eliminated from cells rather quickly, and would not immortalize the

hepatocytes. Accordingly, in the absence of evidence to the contrary, the invention is not fully enabled with the scope of the claims.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14, and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by or in the alternative under 35 U.S.C. 103(a) as obvious over *Jakobovits et al* (USP 6,130,364).

These claims are drawn to a population of hepatocytes that underwent an immortalized and disimmortalized process, wherein the structural limitation for the

claimed hepatocytes would be any hepatocyte containing a heterologus recombinase site, a neomycine resistant gene, and promoter derived from Moloney murine leukemia virus as illustrated in figure 1 of instant specification.

Jakobovits et al teach a transgenic mouse whose genome comprising a homology-targeting vector comprising a loxP site, a neo-R gene (figs. 1-3), and a promoter derived from MoMLV (column 9, line 11), thus the hepatocytes of the mouse meet claim limitation, *Jakobovits et al* anticipate instant claims.

It is noted that the prior art liver cell population differs from the claimed population only by the method of manufacture. However, the claimed hepatocytes would not distinguish structurally over the hepatocytes taught by the prior art because they are genotypically and phenotypically indistinguishable even though the later did not go through the immortalization and disimmortalization processes. The case law teaches, a product-by-process claim may be properly rejectable over prior art teaching the same product produced by a different process, if the process of making the product fails to distinguish the two products (See *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985)). Thus, the claimed invention as a whole was at least *prima facie* obvious, if not anticipated, by the references, in the absence of sufficient, clear and convincing evidence to the contrary.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8, 14, 16-20, 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Nakamura et al* (Transplant 1996;63:1541-7, IDS), in view of *Anderson* (USP 5,629,159, IDS), and *Adams et al* (Proc Natl Acad Sci U S A. 1992 Oct 1;89(19):8981-5).

Nakamura et al teach conditionally immortalized hepatocytes transfected with a replication-defective retroviral vector encoding a thermolabile mutant SV40 T antigen, which confers a reversible immortalization based on the transgene permissive temperature. *Nakamura et al* go on to teach that the transduced hepatocytes significantly improve the survival of rats with acute liver failure (e.g. abstract and fig. 1), and the strategy provides a remedy for the shortage of liver donor in humans (1st paragraph, page 1541, column 2). *Nakamura et al* go on to teach development of this technology for clinical use would require production of hepatocyte cell lines with tighter regulation on the expression of the transforming gene than a simple temperature-sensitive mutation, and suggested to use site-specific recombination to excise the transforming gene from a cell line prior to transplantation (last paragraph, page 1546).

The teaching of *Nakamura et al* differs from instant invention in that it does not physically use the site-specific recombinase for conditional immortalizing the hepatocytes.

Anderson supplemented the teaching of *Nakamura et al* by illustrating the details concerning how to use site-specific recombinase for immortalizing and then disimmortalizing mammalian cells. *Anderson* teaches that the exogenous nucleic acid used in gene therapy is often carried by the cells of a patient's own, and for the purpose of expansion and genetic manipulation, these cells are often immortalized, which may be oncogenic when transplanted back to the patient (Introduction). Accordingly the invention provided methods and cells that may be disimmortalized. *Anderson* discloses a population of immortalized primary murine fibroblast cells transformed with a DNA construct integrated into the genome of said cell, wherein the construct comprises two recombinase target sites (loxP) flanking an oncogene v-myc, (e.g. claim 1, and column 15, lines 11-17), which confers immortalization to said cell; wherein the construct further comprises a selectable marker (e.g. claim 2), and a suicide gene (HPV-tk, column 5, lines 25-38). *Anderson* teaches the immortalization is reversible by introducing a Cre recombinase expression construct into said cell (column 15, lines 61-63, and claims 10-18) and remaining cells containing the oncogene can be destroyed by exposure to gancyclovir. *Anderson* goes on to teach that suitable cells for practicing the claimed invention include any cell type that does not produce a recombinase recognizing the target sequence in the construct, wherein the cells may be obtained from vertebrate, mammalian, and preferably human cells (column 12, lines 32-44). The disclosure of

Anderson differs from the claimed invention in that he does not particularly name or transduce hepatocytes, however, such was suggested by *Nakamura et al.*

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the methods as taught by *Anderson,* in expanding and genetically manipulating hepatocytes as taught by *Nakamura et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the advantage of the immortalization-disimmortalization system as taught by *Anderson* and *Nakamura et al.* Given the success taught by each of the cited references, the skilled artisan would have had a reasonable expectation of success in transducing hepatocytes with the construct as taught by *Anderson*. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Nakamura et al* (Transplant 1996;63:1541-7, IDS), in view of *Anderson* (USP 5,629,159, IDS), as applied to Claims 8, 14, 16-20, 25 above, and further in view of *Adams et al* (Proc Natl Acad Sci U S A. 1992 Oct 1;89(19):8981-5).

The combined teachings of *Nakamura et al* and *Anderson* do not reduced to practice transfecting a human hepatocyte.

Adams et al supplemented the teachings of *Nakamura et al* and *Anderson* by illustrating the feasibility of cultivating and transducing human primary hepatocytes with a retroviral vector construct.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the method as taught by *Nakamura et al* in view of *Anderson,* in expanding and genetically manipulating human primary hepatocytes with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the ultimate goal of conducting animal study was to explore the feasibility of gene therapy in humans as taught by *Adams* and suggested by *Nakamura et al.* Given the success taught by each of the cited references, the skilled artisan would have had a reasonable expectation of success in transducing primary human hepatocytes with the construct as taught by *Anderson*. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

In the remarks filed 6/7/05, the applicant argued that since Adams stated the data from transduction of rodent hepatocytes with amphotropic vectors may not accurately predict the efficiency of transduction of human cells, he de does not provide a reasonable expectation of success.

In response, as an initial matter, except for claim 21, instant claims encompass both rodent and human hepatocytes. Moreover, *Adams et al* clearly acknowledged the differences of transduction efficiency between human cells and rodent cells, and teach, "THE RESULTS DEMONSTRATE THAT HUMAN HEPATOCYTES CAN BE EFFICIENTLY HARVESTED AND CULTIVATED, THAT THESE CELLS WILL PROLIFERATE IN CULTURE, AND THAT THESE CELLS WILL RETAIN LIVER-SPECIFIC FUNCTIONS", and "THE RESULTS ALSO DEMONSTRATE THAT HUMAN HEPATOCYTES CAN BE TRANDUCED WITH AMPHOTROPIC RETROVIRAL VECTORS" (paragraph bridging columns 1

& 2, page 8984), and suggested "WE OBSERVED A HIGHER TRANSDUCTION EFFICIENCY WITH XENOTROPIC VECTORS SUGGESTING THAT XENOTROPIC DETERMINANTS COULD ENHANCE STRATEGIES FOR HEPATIC GENE THERAPY" (last sentence, Introduction). Thus, *Adams et al* teach how to improve the efficiency of transfecting human primary hepatocytes, and do not teach away from practicing instant claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Dave T. Nguyen** can be reached on 571-272-0731. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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QJL
August 18, 2005